The Biomarkers Consortium, update on projects

Quantitative Imaging Biomarkers Alliance (QIBA) Annual Meeting
May 14-15, 2013
Lansdowne Resort, VA

Sonia Pearson-White, Ph.D., The Biomarkers Consortium
Foundation for the National Institutes of Health

The Biomarkers Consortium

Founded in 2006 to develop and qualify biomarkers using new and existing technologies

- Qualifies biomarkers for specific applications in diagnosing disease, predicting therapeutic response, or improving clinical practice
- Addresses a broad range of disease / therapeutic areas
- Generates information useful to inform regulatory decision-making
- Fosters the exchange of knowledge and expertise among industry, academics, and government leaders
- Pre-competitive; makes consortium project results broadly available to the entire scientific community

Our Founding Partners: FDA, NIH, FNIH, PhRMA, BIO, CMS
Value Proposition

The Biomarkers Consortium:

- Facilitates discussions with key opinion leaders and regulatory decision makers
- Provides an integrated approach to cross-sector partnerships across a broad range of disease/therapeutic areas
- Deploys an effective “team science” approach to generate useful consensus science
- Enables sharing of data, resources and expertise across stakeholders to collaboratively address unmet needs
- Employs rigorous, inclusive governance and project management with clearly defined goals and milestones

Contributing Members

For-Profit Companies
- Amgen
- AstraZeneca
- Crescendo Bioscience
- Daiichi Sankyo, Inc
- Eisai, Inc
- Eli Lilly & Company
- Johnson & Johnson
- Merck
- Meso Scale Diagnostics
- Mitsubishi Tanabe Pharma America, Inc
- Myriad RBM
- Pfizer, Inc
- Sanofi
- Takeda Pharmaceuticals USA, Inc

Non-Profit Organizations
- Alzheimer’s Association
- American Diabetes Association
- American Orthopaedic Society for Sports Medicine
- Autism Speaks
- Avon Foundation
- Biotechnology Industry Organization
- Centre for Proteomic and Genomic Research
- CHDI Foundation
- Dairy Research Institute
- Foundation for Health Improvement and Technology
- Juvenile Diabetes Research Foundation
- Pharmaceutical Research and Manufacturers of America
- PROOF Centre of Excellence
- Radiological Society of North America
- US Pharmacopeia
Our Strategic Approach

Our projects address high impact areas of biomarker development and qualification

- **Important**: Address significant unmet scientific and medical needs
- **Translational**: Lead to significant improvements in drug development process
- **Transformational**: Focus on critical gaps and impact on public health / patient care
- **Feasible**: Have goals that are achievable in a specific timeframe
- **Practical**: Leverage pre-existing resources whenever possible
- **Fundable**: Capable of generating required funds and stakeholder support
- **Unique**: Synergistic, do not duplicate other initiatives
- **Collaborative**: Benefit from a multi-stakeholder approach

Governance Structure

- **Executive Committee**: NIH / FDA / CMS / industry / FNIH
- **Cancer Steering Committee**
- **Inflammation & Immunity Steering Committee**
- **Metabolic Disorders Steering Committee**
- **Neuroscience Steering Committee**
- **Multiple Project Teams**: Representatives from NIH, FDA, Industry, Subject Experts from Academia
# Executive Committee

Provides overall steering committee direction and final project approval

Charles Sanders (Chair) FNIH  
Steve Paul (Acting Chair) FNIH

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<thead>
<tr>
<th>FDA</th>
<th>Industry</th>
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<tr>
<td>ShaAvhree Buckman, OTS</td>
<td>Paul Deutsch, Sanofi</td>
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<td>Jeffrey Shuren, CDRH</td>
<td>Gary Herman, Merck</td>
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<td>Janet Woodcock, CDER</td>
<td>Peter Honig, AstraZeneca</td>
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<td>Sara Radcliffe, BIO</td>
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<td>Louis Jacques, CAG</td>
<td>Thomas Insel, NIMH</td>
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<td>Douglas Lowy, NCI</td>
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<td>James Battey, NIDCD</td>
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<td>Garry Neil, Appletree Partners</td>
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<td>Ellen Sigal, Friends of Cancer Research</td>
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# Steering Committee Co-Chairs

Four steering committees identify, develop, approve, and manage portfolios of projects

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<thead>
<tr>
<th>Cancer</th>
<th>Inflammation and Immunity</th>
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<tr>
<td>David Chang, Amgen</td>
<td>Brian Kotzin, Amgen</td>
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<td>Gary Kelloff, National Cancer Institute</td>
<td>Andras Perl, SUNY Upstate Medical</td>
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<th>Neuroscience</th>
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<tr>
<td>Roberto Calle, Pfizer</td>
<td>Linda Brady, NIMH / NIH</td>
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<td>Myrlene Staten, NIDDK / NIH</td>
<td>Husseini Manji, Johnson &amp; Johnson</td>
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The Biomarkers Consortium

- Total projects launched: 15
- Projects completed: 5
- New projects recently approved: 3
- FDA guidances completed with our contributions: 3
- Over $50 Million raised to fund projects: 50
- Journal articles published and mentioned in 50 others: 15

Project Portfolio

Launched Projects

**Executive Committee**
- Kidney Safety Biomarkers
- Skin Infection and Pneumonia

**Cancer**
- FDG-PET in Lung Cancer
- FDG-PET in Lymphoma
- I-SPY 2 Trial

**Inflammation and Immunity**
- Osteoarthritis Biomarkers

**Neuroscience**
- PET Radioligand in Neuroinflammation
- Alzheimer’s Plasma Proteomics
- Alzheimer’s CSF Proteomics
- Alzheimer’s / MCI Placebo Data Analysis

**Metabolic Disorders**
- Adiponectin
- Carotid MRI Reproducibility
- Sarcopenia Consensus Definition
- Atherosclerosis In-Silico Modeling
- Beta Cell Clinical Studies
Project Pipeline

New Project Ideas and Concepts

Executive Committee
- Hospital Acquired Bacterial Pneumonia
- Ventilator Associated Bacterial Pneumonia

Cancer
- Circulating Tumor Cells
- Minimal Residual Disease
- Qualifying Volumetric CT for Clinical Trials

Neuroscience
- Arterial Spin Labeling
- Autism Biomarkers for Drug Development
- PET Imaging for Alzheimer’s Disease

Metabolic Disorders
- Contrast-Induced Acute Kidney Injury
- Obesity
- Outcome Measures for Sarcopenia
- Soluble Markers & Imaging for Bone Quality

Inflammation and Immunity
- Ankylosing Spondylitis
- Functional Decline in COPD
- Lupus Working Group
- TSPO PET Imaging for RA
- CVD/Arthero in Setting of RA

Approved, in funding discussion

The CSC FDG-PET/Volumetric CT Projects in Lung Cancer and Lymphoma

Problem Statement
- With a few additional studies, FDG-PET could facilitate drug development and patient care resulting in shorter duration of Phase 2 studies to evaluate new drug regimen, accelerated approval in Phase 3 trials, with full approval contingent on evidence of clinical benefit and better patient care by ceasing ineffective therapies earlier.

Project Summary
- Two studies, a lymphoma imaging substudy in CALGB 503030 and a lung imaging substudy in ACRIN 6678, are designed to meet these objectives:
  - Establish reasonable minimum standards for FDG-PET acquisition and analysis
  - Build on existing infrastructure for archiving and managing imaging data from multiple sources that will contribute to the qualification program
  - Determine tumor types and drug mechanisms for which FDG-PET may substitute for existing measures of response and outcome during future pharmaceutical trials
  - Prepare initial briefing documents and full data packages for consideration by the FDA Biomarker Qualification Review Team (BQRT)
CSC FDG-PET/Volumetric CT Projects (2)

Project Impact
- FDG-PET is gaining acceptance and use in clinical practice to inform clinical decision-making
- The team has initiated the FDA Drug Development Tool qualification process for FDG-PET in lung cancer and lymphoma, and for Volumetric CT in lung cancer, leveraging additional datasets from several companies

Project Status
- Accrual is complete for the lung study, and will complete in May 2013 for the lymphoma study.
- Data are of high quality and analysis is ongoing.
- 3 year outcomes data will be ready in 2015.

Project Teams
- Lymphoma: Gary Kelloff, MD, NCI (Chair), Wyndham H. Wilson, MD, PhD, NCI (Co-chair and Principal Investigator)
- Lung: Gary Kelloff, MD, NCI (Chair), Wolfgang Weber, MD, MSKCC, (Co-chair and Principal Investigator)

Public-private partnerships

Key elements
- Must provide value for each stakeholder group
- Stakeholder support
- Support from the leadership of the organizations
- Careful, thorough project planning
- Expert, dedicated project management
- Division of labor with no gaps
- Good communication

Benefits
- Sharing the risk
- Cost-sharing, access to different resources
- Greater efficiency
- Improved compliance with regulatory agencies
- Build scientific consensus
- Companies can work together without key concerns, such as:
  - Anti-trust law violation
  - Loss of confidentiality
  - Threats to their IP
The I-SPY 2 project follows and builds on the earlier I-SPY 1 trial

(CALGB INTERSPORCE ACRIN NCICB, CALGB 150007/150012, ACRIN 6657)

Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and And molecular analysis

Five Critical Components of I-SPY 2 Design:

– Neoadjuvant Setting
– Molecular and Imaging Biomarker Guidance
– Adaptive Trial Design
– Multiple Drugs Tested Simultaneously
– Organizational Efficiencies, including IT structure
The ‘Neoadjuvant’ Approach Accelerates Knowledge Turns, As Does The Adaptive Approach

Metastatic Approach: 2 to 4 year knowledge turn
Adjuvant Approach: 6 to 9 year knowledge turn

**Follow-up period**

Years 1 2 3 4 5

Neoadjuvant Approach, chemotherapy before surgery &
Adaptive Approach, 1 year knowledge turn

The I-SPY 2 adaptive trial design stratifies patients into two arms
based on HER2 receptor status; multiple new agents are tested in both arms

Stratifying Biomarkers:
Class I/II devices: HER2 (IHC, FISH)
MammaPrint
ER, PR
IDE:
MammaPrint44K
Her2 (RPMA, 44K-microarray)
The Eight Biomarker Subtypes (HR+/-, HER2+/-, MP H2+/-) Are Grouped Into Ten Combination “Signatures” based on Stratifying Biomarkers

<table>
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<tr>
<th>MP1</th>
<th>MP2</th>
<th>Biomarker Signature</th>
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• "X" indicates that the respective disease subtype is included in that signature.
• "Signature #7 is called "triple negative" because ER, PR, and HER2 are all negative.
• Estimated prevalences are from I-SPY 1.
• Signatures overlap

- Treatment assignments will be made based on which of the eight (=2x2x2) subtypes characterizes each tumor.
- The utility of each treatment regimen will be evaluated for these ten biomarker signatures, not within individual subtypes

Biomarkers in I-SPY 2

**Stratifying Biomarkers**
- **HER2**
- **HR**
  - ER
  - PR
- **Mammaprint™**
  - MP1
  - MP2 ≥ median score of patients in I-SPY 1
  - Low, excluded from trial unless ER+ HER2+

**Qualifying Biomarkers**
- Panomics mRNA expression arrays (UCSF)
- RPMA (reverse phase protein microarrays, at GMU)
- GWAS, SNPs, genomics, pharmacogenomics (UCSF)
- MRI Imaging, MR Volume

**Exploratory Biomarkers**
- Additional, new assays per Biomarker Committee decision
- e.g. CTCs
- e.g. miRNAs

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MR Imaging in the I-SPY 1 and 2 Breast Cancer Trials

I-SPY 1
Standard AC/T

ACRIN 6657 Original 2002
Contrast enhanced breast MRI for measuring response and predicting 3-yr RFS

ACRIN 6657 Extension 2007
Choline (tCho) measured by MRS for early prediction of response

I-SPY 2
T + novel agent

ACRIN 6698 (May 2012) 2010
Multi-parametric MR imaging markers (ADC, SER) for measuring response to targeted agents

ISPY1 - ACRIN 6657
Contrast-enhanced breast MRI for evaluation of patients undergoing neoadjuvant treatment for locally-advanced breast cancer

Volumetric assessment of tumor response based on enhancement criteria (SER)

• MRI provides better prediction of pathologic complete response (pCR) than clinical assessment, with the greatest relative benefit early in treatment.

Hylton et. al. Radiology 2012

AUC comparison of MRI and clinical size for predicting pCR
Hologic/Sentinelle AEGIS SER Plug-in
IDE-approved software for I-SPY tumor volume calculation

- Image data transferred from scanner to AEGIS workstation
- Technologist or RA places boxes on 2 views (sagittal and axial)
- AEGIS runs volume calculation and automatically generates report

*developed under NCI Academic-Industrial Partnership (AIP) Grant “Real-time in vivo MRI biomarkers for breast cancer pre-operative treatment trials” (R01 CA132870)
Primary Aim: To determine if early change in tumor ADC value is predictive of pathologic complete response.

Advances in ISPY-2 Imaging

- Protocol compliance and image quality monitoring
- “Real-time” volume measurement software deployed on a commercial platform (Hologic/Sentinelle AEGIS platform)
- Diffusion-weighted MRI added to the imaging protocol (ACRIN 6698)
  - 4 b-value DWI
  - Specialized techniques will be added at select sites (ie. high-res DWI)
- New computational tools to optimize imaging biomarker performance
Drugs graduate from I-SPY 2 with a biomarker profile that should allow Phase II testing in fewer patients, accelerating approval

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

**Traditional clinical trial**
- Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.
- New trial design uses genetic profiles to highlight "biomarker" differences among patients and to match drugs to patients with biomarkers that predict a benefit.

**Wall Street Journal 2010**

**I-SPY 2 Organizational Principles, Efficiencies**

- I-SPY 2 is collaborative by design
  - involved stakeholders from the beginning, FDA, NCI, investigators, companies, patient advocates
- Simultaneous development of the protocol, master IND, IT infrastructure, site selection, agent selection
- FNIH-managed (including project management, contracts, fundraising)
- Master IND (held by FNIH) incorporates testing of multiple agents
- Safety – DSMB meets monthly
- IT infrastructure builds on caBIG

Communications
- www.ispy2.org website
- brochure
FNIH acts as a trusted third party to ensure fair and appropriate licensing of new inventions arising from I–SPY 2

1. Inventing Organizations grant exclusive licenses to new IP to FNIH

2. FNIH prosecutes and manages resulting patents

3. FNIH markets and licenses IP to interested parties

4. FNIH returns a fair share of royalties (less expenses) to Inventing Organizations

Everyone Works Together As A Team

- PIs, Data, Design: Don Berry, Laura Esserman
- Imaging: Nola Hylton
- Biomarkers: Laura van’t Veer
- Operations: Angie DeMichele
- Agent Selection: Doug Yee
- Informatics: Mike Hogarth
- Pathology: Fraser Symmans
- Advocates: Jane Perlmutter
- Project Management: Meredith Buxton, Quantum Leap, FNIH
- NCI Leadership: Anna Barker, Gary Kelloff
- FDA, CDER Leadership: Janet Woodcock, Karen Weiss
- FNIH Leadership: David Wholley, Sonia Pearson-White
- Pharma, Biotech: Abbott, Amgen, Merck, Agenda, Pfizer, Genentech, Sentinelle/Hologic, Puma + others
- Local Sites: Coordinating multi-disciplinary teams for 1 study
- Local IRBs: Collectively working on trial regulatory challenges
- CRO: Quintiles, Inc.
I-SPY 2 Progress

Sites
- 18 sites now enrolling
- 2 more sites being added

Agents
- 5 in the trial
- Randomization is adaptive
- 2 in near term pipeline
- ~12 more under consideration

Accrual
- Accrual on target
- 713 enrolled and screened
- 377 randomized to treatment
- 305 completed
- >10,000 biospecimens collected to date

As of 4/15/13

FDA Issued Draft Guidance Concerning Elements Of The I-SPY 2 Trial Design


Guidance for Industry
Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

For questions regarding this draft document contact Tatiana Prowell, M.D. at 301-796-2330.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)
May 2012
Clinical/Medical

NEJM Perspective published May 30, 2012
Thank You

Contact information:
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- Websites: www.ispy2trial.org and for patients, www.ispy2.org
- www.biomarkersconsortium.org and www.fnih.org